Early detection of lung cancer: A statement from an expert panel of the Swiss university hospitals on lung cancer screening

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Early Detection of Lung Cancer: A Statement from an Expert Panel of the Swiss University Hospitals on Lung Cancer Screening

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Key Words
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Abstract
The discussion about setting up a program for lung cancer screening was launched with the publication of the results of the National Lung Screening Trial, which suggested reduced mortality in high-risk subjects undergoing CT screening. However, important questions about the benefit-harm balance and the details of a screening program and its cost-effectiveness remain unanswered. A panel of specialists in chest radiology, respiratory medicine, epidemiology, and thoracic surgery representing all Swiss university hospitals prepared this joint statement following several meetings. The panel argues that premature and uncontrolled introduction of a lung cancer screening program may cause substantial harm that may remain undetected without rigorous quality control. This position paper focuses on the requirements of running such a program with the objective of harmonizing efforts across the involved specialties and institutions and defining quality standards. The underlying statement includes information on current evidence for a reduction in mortality with lung cancer screening and the potential epidemiologic implications of such a program in Switzerland. Furthermore, requirements for lung cancer screening centers are defined, and recommendations for both the CT technique and the algorithm for lung nodule assessment are provided. In addition, related issues such as patient management, registry, and funding are addressed. Based on the current state of the knowledge, the panel concludes that lung cancer screening in Switzerland should be undertaken exclusively within a national observational study in order to provide answers to several critical questions before considering broad population-based screening for lung cancer.

Introduction

Recently published data from the National Lung Screening Trial (NLST) showed a 20% reduction in lung cancer mortality in subjects who underwent CT screen-

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Table 1. Potential benefits and harms of lung cancer screening

Benefits	Harms
Mortality reduction	Unnecessary diagnostic procedures and procedure-related complications (due to the high number of false-positive findings)
Improved quality of life (in case of early detection)	Radiation exposure
Smoking cessation	Overdiagnosis Anxiety and impaired quality of life (due to false-positive results) False sense of reassurance and thus continuation of smoking (in case of a normal CT scan)

ing compared to those randomized to conventional chest X-ray [1]. In Europe, several randomized controlled studies using low-dose CT (LDCT) as a screening tool for the detection of lung cancer have been or are still being performed [2–7]. The largest among these European randomized LDCT screening trials, i.e. the Dutch-Belgian NELSON Trial, started in 2003 and the final results are awaited [5, 6].

Several associations and panels released statements on whether or not to implement lung cancer screening in clinical practice after the publication of the results of the NLST [8–13]. Some of these statements highlighted the need for further improvement of CT screening and describe specific areas which should be addressed in guidelines and recommendations [11, 14–16]. In contrast, other associations suggested that screening should be immediately implemented [17, 18]. Despite the positive results of the NLST, we think that the following points need to be established before large-scale lung cancer screening programs with LDCT can be implemented in the clinical routine: the definition of the population at risk, the variability of radiological standards and adapted guidelines for use in national screening programs, the number and frequency of screening rounds, the additional value of lung nodule volumetry versus 2-D measurement, the development of appropriate guidelines for the clinical workup of 'indeterminate nodules' resulting from CT screening programs, the quality of life including the psychological consequences of taking part in such a program, the role of smoking cessation intervention, and questions related to costs and cost-effectiveness [15, 19].

The discussion about lung cancer screening has also started in Switzerland [20]. The SUVA (Schweizerische Unfallversicherungsanstalt), an independent, nonprofit company under public law, started a screening program for patients with a history of asbestos exposure shortly after the publication of the results of the NLST although there is no evidence from randomized controlled trials that lung cancer screening is effective in such a population. This program involves private physicians and is running in many radiology departments without any quality control. Other private institutes have also started to advertise lung cancer screening. In June 2012, a first meeting of several stakeholders representing the Swiss university hospitals took place in an attempt to constitute a national expert panel to address open questions related to lung cancer screening programs. The expert panel prepared this statement paper on the topic, mainly focusing on practical issues related to lung cancer screening with LDCT, with the awareness that smoking cessation is the most efficient method to reduce the number of lung cancer cases. Other important issues such as alternative methods of lung cancer screening and the implications of screening for therapeutic decisions or socioeconomic aspects are only briefly or not addressed. The panel agreed that, at present, lung cancer screening should be performed exclusively in the framework of an observational study accompanied by a prospective registry to ensure quality control and to generate longitudinal observational data on aspects of screening-related harm (table 1) and to assess the feasibility, the quality, and especially the direct and indirect costs and cost-effectiveness of such an intervention.

The purpose of this paper is to provide information on how such a study on lung cancer screening with LDCT should be implemented in Switzerland. At this point, it seems important to harmonize efforts across the involved specialties and institutions, to define quality standards, and to develop the appropriate study methodology.

Epidemiology and Effectiveness of Lung Cancer Screening Programs

Worldwide, lung cancer is the most commonly diagnosed cancer (12.7% of all cancers) and, because of its high fatality rate, the most common cause of death from cancer [21]. Poor 5-year survival rates (16%) are related to advanced disease at diagnosis [30% Union for International Cancer Control (UICC) stage III and 40% stage IV] [22]. In Switzerland, annually 2,500 men (13% of all cancers) and 1,700 women (8% of all cancers) are diagnosed with lung cancer and 2,000 men (23% of all cancer deaths) and 900 women (13% of all cancer deaths) die from lung cancer [23]. While in men the incidence rate declined in Switzerland between the 1980s and 2007, the incidence of lung cancer in women almost doubled within the same time span and is now reaching a plateau.

Earlier studies showed that lung cancer screening studies with conventional chest X-ray and sputum cytology detected more lung cancers, earlier cancer stages, and smaller tumors, but there was no reduction in late-stage tumors and lung cancer-specific mortality [16, 24–35]. With its introduction approximately one decade ago, LDCT enhanced the detection of lung cancer [36].

According to a recent systematic review that analyzed the data of 8 randomized controlled trials and 13 cohort studies to assess the possible benefits and harms of lung cancer screening, lung cancer-specific mortality was only reported in 4 trials (Detection and Screening for Early Lung Cancer by Novel Imaging Technology and Molecular Assays (DANTE) [2], NLST [1], Danish Lung Cancer Screening Trial (DLCST) [4], and MILD Trial [7]) [16]. Of these, the NLST randomized 53,439 smokers and ex-smokers aged 55–74 years to an annual conventional chest X-ray or LDCT over 3 years [1]. After a median follow-up duration of 6.5 years, the NLST found a reduction in lung cancer-related mortality of 20% in the LDCT screening group compared to the chest X-ray group. The authors calculated that 320 individuals needed to be screened by LDCT to prevent 1 lung cancer-related death. In contrast, the smaller DLCST [4] and the DANTE Trial [2] found no significant mortality reduction with 5 annual rounds of LDCT compared to the usual care at a median follow-up of 34 and 58 months, respectively. Furthermore, no statistically significant positive or negative effects on smoking behavior have been observed in any of the LDCT lung cancer screening trials to date.

The radiation exposure of a single LDCT examination is about 4- to 5-fold and 9- to 10-fold lower than the values of conventional chest CT and PET-CT, respectively [37, 38]. However, a screening program with several LDCT examinations may substantially increase the cumulative radiation exposure; for example, an estimated average of 8 mSv was delivered in the NLST due to screening and diagnostic investigations [1, 16]. Using exposure models, Bach et al. [16] estimated that radiation exposure from the NLST would result in 1 cancer death for every 2,500 individuals screened. The authors concluded that in the NLST population the decrease in mortality due to screening outweighed the risk of radiation, but in individuals younger than 42 years or in those at a lower risk for lung cancer this may not be the case [16, 39]. According to the calculation of Bach et al. [16], the cumulative 10-year risk for the diagnosis of lung cancer in participants meeting the minimum entry criteria and based on the assumption that they had quit smoking at the time of study entry was approximately 2% for the NLST. Although screening programs may improve the quality of life thanks to the reduced lung cancer-related morbidity associated with advanced disease, they may also generate anxiety and discomfort, thus potentially causing harm [16]. The Dutch-Belgian NELSON Trial included 15,822 subjects. Half of them were randomized to the LDCT arm. Screening was performed at baseline and 1, 3, and 5.5 years later (4 rounds) with a 10-year follow-up period [5, 6]. In a subgroup analysis of 351 participants, 87–99% (depending on the specific questionnaire used) of individuals experienced no discomfort due to CT, but 46% were distressed awaiting the CT results [40].

Screening Population

Definition of the population to be screened is a challenging task and requires careful balancing of the benefits and harms of a screening program. As discussed above, the benefit/harm balance depends substantially on the absolute risk of these outcomes. Therefore, lung cancer screening programs should focus, like other screening programs, on the population at increased risk for the disease to be prevented and exclude people in which the benefit-harm balance is unlikely to be favorable (e.g. a lung cancer screening program in people with no smoking history or less than 10 pack-years where the number needed to screen would be too high). For example, the NLST focused on subjects between 55 and 74 years of age with a cigarette smoking history of at least 30 pack-years without evidence of lung cancer (e.g. hemoptysis or unexplained weight loss in the preceding year). The Early Lung

Cancer Action Project (ELCAP) defined its population similarly [41]. In the NLST population, the number needed to screen to prevent 1 lung cancer death out of 320 persons undergoing 3 annual CT scans compared to no CT scans [1] needs to be contrasted with the harm in this population. The NLST reported overall mortality and major complication rates after diagnostic procedures for benign nodules in the LDCT group of 4.1 and 4.5 per 10,000 participants, respectively, compared to 1.1 and 1.5 per 10,000 in the chest X-ray group [1, 16]. Additionally, screening may identify lung cancer that would not have affected the patient's life if left untreated, a phenomenon termed overdiagnosis [42]. Bach et al. [43] addressed the problem of overdiagnosis in 2007 using calculations based on CT screening. They showed that, despite the fact that more tumors were detected by CT screening, the numbers of advanced tumors and tumor related deaths were not reduced. Other studies based on X-rays as well as one recent study on LDCT have reported an overdiagnosis rate of about 25% [16, 44–46]. The findings of the NLST suggested that overdiagnosis might have occurred, but due to the study design this cannot be ascertained and quantified at this stage.

Evidence of both the benefits and the harms of early lung cancer detection programs is still scarce and therefore it is currently difficult to define a population other than the one defined by the NLST in which the benefit-harm balance of lung cancer screening is likely to be favorable. A recent study by Kovalchik et al. [47] analyzed the NLST population concerning their risk of developing lung cancer and showed that in subjects with multiple risk factors the benefit clearly outweighs the harm. The findings of this analysis possibly call for individual risk stratification in lung cancer screening programs, which is likely to improve the cost-effectiveness of LDCT screening [47]. Also, the most appropriate number of screening rounds is uncertain at this stage. Therefore, we suggest that, if screening is performed, the screened population should be the same as in the NLST, focusing on individuals aged 55–74 years with at least 30 pack-years of smoking history, either active or discontinued for less than 15 years, with no clinical symptoms of lung cancer. The recommendation of extending the screened population to other age groups, to patients with COPD, to those with a previous history of lung cancer, or to those with a lower level of smoking exposure [17] is not supported by the current evidence, it is likely to be harmful, and it should therefore be avoided. Recent studies suggest that the selection criteria for lung cancer screening can be refined [48].

Minimal Requirements of a Lung Cancer Screening Center

Performed within a national prospective trial or registry, we propose that lung cancer screening should only be done at institutions with the necessary infrastructure and expertise for the multidisciplinary workup of lung nodules and management of lung cancer, which are most likely to replicate the results of the NLST [14, 15, 49, 50]. These requirements should be enforced by the health authorities similar to the screening program for breast cancer and should adhere to standards for training, infrastructure, procedures, and documentation including the following:

- A chest imaging unit with low-dose HRCT (for the minimum technical requirements, see Technique and Algorithm of Lung Nodule Assessment), percutaneous CT-guided needle biopsy, and PET-CT
- A respiratory medicine unit with state-of-the-art cardiopulmonary exercise testing facilities and video bronchoscopy
- A cytopathology department
- A thoracic surgery unit experienced in minimally invasive surgical techniques
- Comprehensive pre- and postoperative care, including an intensive care unit and pulmonary rehabilitation
- An oncology unit with organ-specific multidisciplinary tumor boards on a routine basis
- A smoking cessation program and counseling

All specialists involved should be board certified in their respective disciplines.

Patient information on lung cancer screening should be provided both orally and in written form with the help of specific information material. The patients are assessed according to the NLST criteria, which does not provide an explicit risk prediction for lung cancer but restricts the screening to a population at increased risk for lung cancer compared to subjects who, for example, smoked less or are outside of the age range used in the NLST [47, 50, 51]. The information material should provide key data about the expected screening benefits and harms in a neutral and nonpersuasive way [14], including an explanation of the difference between a screening test and a diagnostic procedure, the facts that screening will not detect all cancers, that screening is more likely to detect a benign abnormality than cancer, and that the benefit-harm ratio is still unclear, and the potential risks of invasive diagnostic and therapeutic procedures [13, 15]. A flowchart may be provided showing the possible scenarios [49]. Sufficient time should be allowed for decision making and the first screening CT should not be performed on the same day

the information is provided. Smoking cessation programs are to be systematically integrated. After a negative screening round, patients should be informed of the symptoms of lung cancer [15].

Institutions performing lung cancer screening should adopt an ethical chart stating that they do not recruit patients through direct or indirect advertisement, use fear of cancer to promote lung cancer screening, let patients believe that the cancer risk can be eliminated by screening, or offer screening at reduced costs with the aim of generating profit from additional diagnostic and therapeutic procedures [50].

Technique and Algorithm of Lung Nodule Assessment

Imaging Protocol

For lung cancer screening, at best a 64-slice multidetector CT scanner or a later generation scanner should be used. This is to achieve the optimal spatial resolution for accurate and reproducible measurements of small nodules. The slice thickness should be 1.5 mm or less and imaging has to be performed without contrast in full inspiration. A low-dose protocol must be used with an effective dose of around 1 mSv depending on the patient's weight and including iterative reconstruction whenever possible.

Lung Nodule Assessment

A lung nodule is defined as a small, approximately spherical, nonlinear, circumscribed focus of abnormal soft tissue [52, 53]. Lung nodules can be categorized as calcified nodules in the presence of a benign pattern of calcium, assolid nodules if they have areas of homogeneous soft tissue attenuation, as partly solid nodules if they have both solid and ground-glass attenuation, and as nonsolid (pure ground-glass) nodules if they only have ground-glass attenuation. Although the shape of a solid lung nodule may add to the evaluation regarding its potential malignancy, the size or volume of the nodule should preferably be used as the objective criteria [54–56].

The expert panel proposes employment of the algorithm outlined in the statement of the National Comprehensive Cancer Network (NCCN) for the management of solid nodules and partly/nonsolid nodules [9]. In case of new nodules detected at the annual or follow-up LDCT, the algorithm for the management of solid nodules and partly/nonsolid nodules should be applied in cases of no suspected infection. The workup for solid nodules should be in accordance with the Fleischner Society criteria [57]. There are new recommendations from the Fleischner Society regarding the management of subsolid nodules, which still need to be integrated into the current algorithm [58]. For nonsolid nodules, the guidelines follow the recommendation of Godoy and Naidich [59]. Although in all running screening programs size is the most important factor, results from the NELSON Trial, for example, show that perifissural nodules are mostly benign and do not need further workup even if they are growing [54, 60]. In cases of suspected infection, a follow-up LDCT should be considered after 6–8 weeks and if the nodules increase in size a diagnostic workup is necessary.

Though all of these algorithms utilize the mean nodule diameter as the only relevant criterion, the largest European lung cancer screening trial, i.e. the NELSON Trial, focused on the volume and the change in volume as the major criteria for lung nodule assessment and further management [6]. French experts of the French intergroup (IFCT) and the Groupe d'Oncologie De Langue Française (GOLF) also adopted such an approach [10]. The volumetric analysis may allow a more accurate and more differentiated assessment of lung nodules. The preliminary results of the NELSON Trial suggest that volumetry of the nodule may be a useful parameter to reduce the false-positive and false-negative rates, but this technology is not widely available yet [6]. Nevertheless, the panel advocates the use of lung nodule volumetry in the case of a standardized CT protocol and use of the same software for each measurement.

Computer-assisted detection (CAD) of lung nodules has recently become more important. Several studies have shown that the use of CAD in radiological practice can significantly improve the diagnostic accuracy of pulmonary nodule detection [61, 62]. In an analysis based on data from the NELSON Trial, the sensitivity of CAD to detect lung nodules was 96.7% compared to 78.1% for conventional double reading without CAD [61]. This difference seems to be particularly explained by the observation that nodules attached to vessels are often missed by conventional reading. Therefore, the panel advocates the use of a CAD system as a second (or additional) reader in a lung cancer screening program. No benefit has been shown for double reading [63].

Workup of Solid Nodules. If malignancy is highly probable, then the nodule should be surgically removed. PET-CT as a single method has a negative predictive value of only 81% as shown by van't Westeinde et al. [64], which is insufficient to rule out malignancy. However, the findings

of other studies suggest that PET-CT can be used to reduce the number of false-positive findings, especially when used in combination with other diagnostic procedures [65, 66]. Accordingly, Ashraf et al. [66] found that the use of both PET and the volume doubling time increases the sensitivity and specificity for lung cancer diagnosis to 90 and 82%, respectively.

Workup of Subsolid Nodules. The management of subsolid nodules should be based on the recommendations of the Fleischner Society [58]. As shown in the MILD Trial, the growth rate of subsolid nodules is usually very low, and thus active prolonged surveillance is recommended [67]. This may be adapted according to the type of subsolid nodule, the initial nodule size, and the past history of lung cancer [68]. In fast growing ground-glass lesions, PET has rarely been proven to predict malignancy, and thus surgery is often the diagnostic strategy of choice [55, 59, 69].

Besides lung cancer-related mortality, the NLST also found a 6.7% decrease in all-cause mortality [1]. There are several pathologies that may be found when an LDCT is being performed and this may affect mortality. Graham et al. [70], for example, showed that a diagnosis of severe coronary calcification has a significant impact on mortality. It is therefore possible that analysis of imaging features other than lung nodules may have an impact on survival or other clinical outcomes. The relevance of these additional findings has been investigated by several groups [71–73]. In all of these studies the number of significant incidental findings did not exceed 7%. This was influenced by the wider scan range in that population, covering parts of the upper abdomen [72]. Priola et al. [72] estimated that the additional incurring costs might not be extensive. However, currently there is no consensus on whether or not these incidental findings should be reported. This has also been discussed based on data of the NELSON Trial, and van de Wiel et al. [71] advised against systematic reporting of all incidental findings.

Patient Management

Infrastructural Needs and Organization

The individual management of patients participating in a lung cancer screening study is of crucial importance. Dedicated, well-trained medical and paramedical staff embedded within a well-organized infrastructure is the key to running an efficient lung cancer screening program. The required infrastructure for such a center as well as how participants should be informed is discussed in more detail in Minimal Requirements of a Lung Cancer Screening Center.

The core facility for patient management should be a dedicated outpatient clinic within a chest unit to guarantee high-quality patient counseling and treatment. In addition, the patient flow and the interaction between the several involved medical specialties and the referring GP are key issues that need to be precisely defined in written protocols. Figure 1 summarizes a possible workflow for the management of patients.

Interaction between Radiologists, Pulmonologists, and Other Specialists

Interaction between specialists becomes important if a CT scan is abnormal. In weekly interdisciplinary meetings (radiology, pulmonary medicine, and thoracic surgery) any pathological CT finding requiring further investigation should be discussed. Lung nodules for which a CT follow-up is planned within the screening process do not necessarily need interdisciplinary assessment.

The joint decision of the interdisciplinary assessment team on the necessary further diagnostic or therapeutic steps should be documented in writing and constitute the basis upon which the chest unit discusses the findings of the CT scan with the patient.

Communication of Pathological Findings to the Patient, Coordination of Further Diagnostic Steps, and Communication with the Referring Physician

The chest unit should discuss all pathological findings described by the radiologist (this also includes extrathoracic findings) with the patient during a medical appointment. A letter detailing the results of the CT scan and recommendations regarding further investigations and/or follow-up CT screening should be forwarded to the referring physician, the patient, and members of the interdisciplinary assessment team. The chest unit may organize further investigations. It is important that the chest unit play an active role in the management of the patient in accordance with the referring physician.

Smoking Cessation

All participating patients should be advised to cease smoking and they should be actively encouraged to participate in a structured smoking cessation program. Counseling and referral should be repetitiously offered to the participant whenever she/he is seen in the chest unit. Smoking cessation programs should follow international recommendations, for instance those of the Centers for Disease Control and Prevention [74].

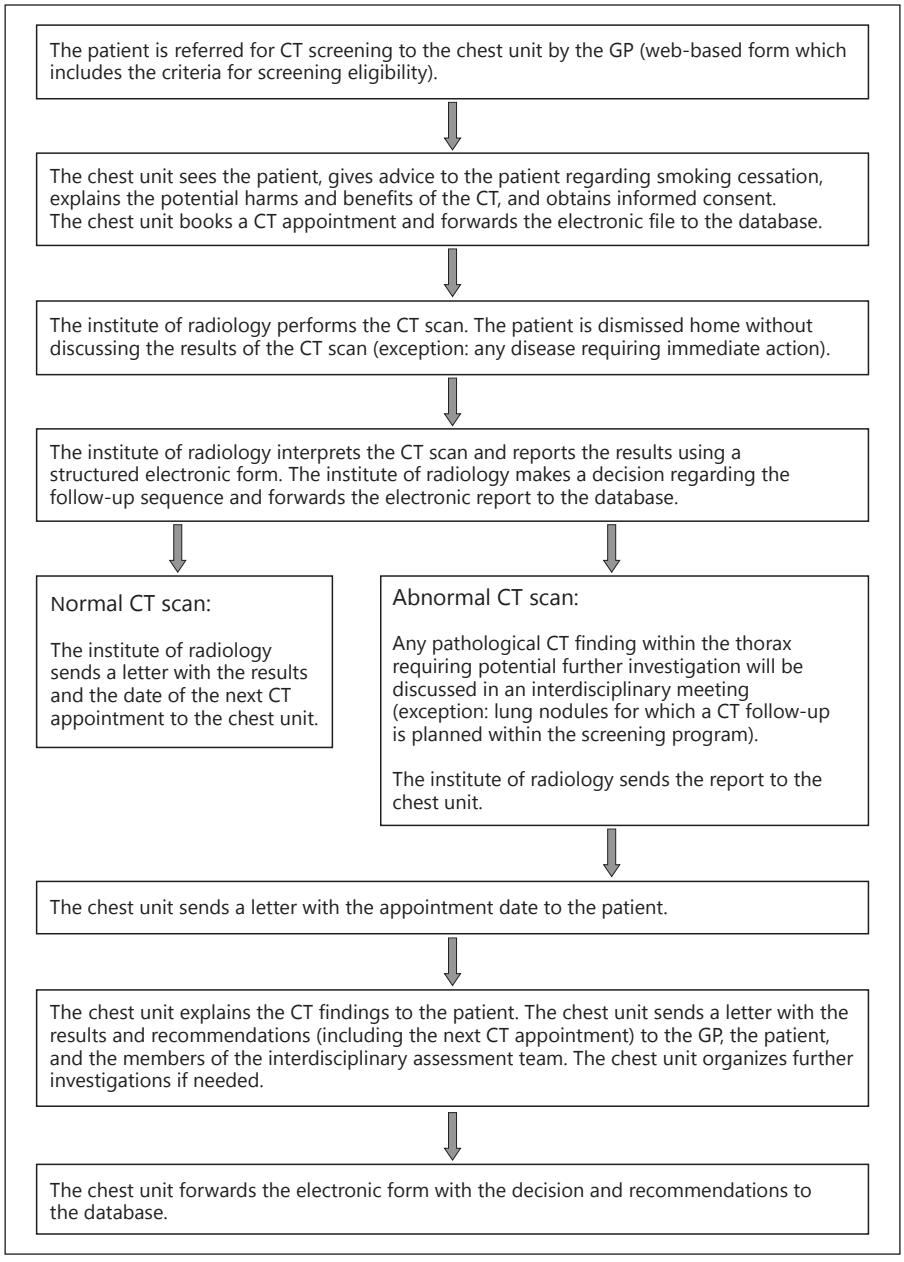

Fig. 1. Summary of a possible workflow for the management of patients.

Costs and Cost-Effectiveness

In the NLST, 320 patients needed to be screened to avoid 1 cancer death. McMahon et al. [75] assessed the cost-effectiveness of the NLST comparing the estimated quality-adjusted life years (QALY; measurement of the disease burden, including the quality and quantity of life lived) for lung cancers based on the screening test to either no intervention or the addition of a smoking cessation program for both study arms [75]. In the latter publication, the calculated costs ranged between USD 126,000 and USD 169,000 per QALY for current and former smokers aged 50–74 years with a smoking history of at least 20 pack-years. If only subjects with at least 40 pack-years were included in the analysis, the costs were reduced to a range between USD 110,000 and USD 166,000 per QALY. If linked to a smoking cessation program with an assumed background cessation rate of 6%, the costs were estimated to be USD 75,000 per QALY for subjects aged ≥50 years and at least a 20-pack-year smoking his-

tory. A comparison of these data with the cost of colorectal screening (USD 13,000–32,000 per QALY) or breast cancer screening by mammography (USD 47,700 per QALY) implies that the population to be included in a lung cancer screening program needs to be defined very carefully. Another study by Goulart et al. [76] calculated that LDCT screening will avoid 8,100 premature deaths from lung cancer at a cost of USD 1.3–2 billion in annual national health care expenditures in the USA. Thus, the additional cost of screening to avoid 1 death would be USD 240,000. In summary, to date no study has been able to show that LDCT screening is cost-effective. Further analysis of the NLST may determine whether lung screening is cost-effective; however, these estimations largely depend on the parameters and assumptions used. For example, Pyenson et al. [77] calculated that the cost per life year saved would be below USD 19,000, which is comparable to the cost of mammography screening (USD 18,000).

The cost of an LDCT and 2 outpatient appointments is approximately CHF 270–350 and CHF 250, respectively, based on the Swiss health tax system (TARMED), thus resulting in a direct cost of one screening round of approximately CHF 520–600. However, these direct costs are only a fraction of the total incurring costs, as the diagnostic workup and treatment related-costs cannot be reliably predicted from the available data. It is therefore crucial to gain more knowledge of these costs, not only for the health authorities but also for insurance providers.

Call for a National Registry

Quality maintenance is the ongoing process of establishing and improving the standards for all components of a program. In a multidisciplinary setting, monitoring of quality is critical for the success of a lung cancer screening program. Comparison of practices and outcomes between screening centers is needed to guarantee high-quality standards at a national level. We therefore suggest setting up a common national registry with the following goals:

- To characterize the population that undergoes lung cancer screening. This should ensure that only eligible subjects are included and not those who do not, according to the current evidence, qualify for the program.
- To monitor the adherence to quality standards for all steps of the program. Quality indicators should be collected for the initial encounter where subjects are informed about the potential harms, for the screening CTs, for the invitation and adherence to a smoking cessation program, and for the follow-up diagnostic and therapeutic procedures that follow the screening CTs.
- To collect short-, mid-, and long-term data on benefit and harm outcomes.
- To evaluate the costs and cost-effectiveness not only of the screening procedure itself but also of all consecutive costs.

Such a registry is a central element for quality assurance and would provide a basis for detecting deviations from standardized procedures and a comparison of outcomes with those of the NLST and other studies. Also, comparisons of quality and outcomes across centers and over time need to be performed. These data would be required to inform the decision of whether and how to implement a lung cancer screening program in Switzerland, as well as for discussions with legal authorities and health insurances. However, as the proposed study design would be a purely observational study without a control group, it will not be possible to assess the efficacy of CT screening regarding the reduction of lung cancer mortality.

Conclusion

Lung cancer is a lethal disease associated with substantial medical and economic burdens. The NLST is currently the only randomized trial that has shown that lung cancer screening may reduce mortality, and the results of the NELSON Trial are eagerly awaited. The possible advantage of LDCT screening has to be balanced against the potential of inducing harm. Despite the benefit of early lung cancer detection and the prevention of tumor-related deaths, LDCT screening may produce harm, e.g. through unnecessary biopsies, radiation exposure, and psychosocial stress. Before lung cancer screening can be broadly implemented in clinical practice in Switzerland, these critical issues have to be addressed appropriately. Therefore, based on the current evidence it seems important to stress that lung cancer screening should be exclusively performed in the setting of an observational study organized by skilled professionals, in institutions with the appropriate infrastructure and expertise, and based on recommendations set forth by harmonized guidelines and standardized procedures.

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